Sex hormones and injury in female athletes

Umile Giuseppe Longo [1,2], Aurora Citerni di Siena [2], Ginevra Andreucci [2], Alessandro de Sire [3,4], Silvia Migliaccio [5], Umberto Tarantino [6], Pieter D'Hooghe [7], Sports Committee OrtoMed [1,2]

[1] Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy; [2] Research Unit of Orthopaedic and Trauma Surgery, Department of Medicine and Surgery, Università Campus Bio-Medico di Roma, Rome, Italy; [3] Department of Medical and Surgical Sciences, University of Catanzaro "Magna Graecia", Catanzaro, Italy; [4] Research Center on Musculoskeletal Health, MusculoSkeletalHealth@UMG, University of Catanzaro "Magna Graecia", Catanzaro, Italy; [5] Department of Experimental Medicine, Section of Endocrinology and Nutrition, "Sapienza" University of Rome, Rome, Italy; [6] University "Nostra Signora del Buon Consiglio", Tirana, Albania; [7] Aspetar Orthopedic and Sports Medicine Hospital, Aspire Zone, Doha, Qatar;

ABSTRACT

Background: Sex hormones regulate musculoskeletal tissue properties, influencing bone and muscle health, and injury risk and recovery in female athletes. Hormonal fluctuations during the menstrual cycle, pregnancy, and menopause affect tissue homeostasis and injury susceptibility.

Purpose: This narrative review synthesizes current evidence on the effects of oestrogens, androgens and progestogens on musculoskeletal health, injury risk, and prevention strategies in female athletes. It also examines the impact of hormonal modulation, including oral contraceptive use.

Methods: A literature search was conducted across peer-reviewed databases, focusing on studies from the past two decades. Both preclinical and clinical studies were included, addressing the physiological effects of sex hormones on bone and muscle, injury mechanisms, focusing in particular on anterior cruciate ligament (ACL) and Achilles tendon injuries, and preventive strategies.

Results: Oestrogens are crucial for bone density and turnover; their deficiency increases fracture risk. Androgens promote cortical bone formation, while progesterone supports the action of oestrogens. In skeletal muscle, oestrogens improve contractility, reduce inflammation, and aid repair; while progestogens—via their active form, progesterone— enhance protein synthesis and endurance. Low oestrogen states are linked to higher injury risk. Oral contraceptives, by stabilizing hormone levels, may reduce ACL injury risk but have been associated with increased Achilles tendinopathy. Exercise-based, multicomponent prevention programmes tailored to female physiology significantly reduce injury incidence in women.

Conclusions: Sex hormones are central to musculoskeletal health and injury risk in female athletes. Preventive and training strategies should take hormonal status into account to optimize performance and reduce injuries. Further research is needed to better understand the effects of hormonal modulation and to refine preventive approaches.

KEYWORDS

Sex hormones, musculoskeletal tissue, bone health, muscle function, injury risk, ACL injury, Achilles tendinopathy, oral contraceptives, female athletes, injury prevention.

The physiology of sex hormones

Sex steroids are hormones synthesised by the gonads, adrenal glands, and, to a lesser extent, peripheral tissues. They are primarily involved in the development of the reproductive system and the expression of primary and secondary sex characteristics, but have also been shown to influence various non-reproductive organs [1].

All sex steroids derive from the cholesterol biosynthetic pathway, and therefore share a similar chemical backbone. Sex hormones can be classified into androgens (19C), oestrogens (18C), and progestogens (21C), according to the number of carbon atoms they contain [2]. Oestrogens and progestogens are the key female hormones, while androgens are principally male hormones; however, females also produce androgens in the ovarian stroma and adrenal zona fasciculata, although at concentrations ten times lower than males [2].

Oestrogens are mainly synthesised by the placenta and the corpus luteum of the ovary, with smaller contributions from adipose and other peripheral tissues. They regulate the development of the female reproductive system and the expression of secondary sex characteristics. The most biologically active oestrogens are oestradiol (E_2), estrone (E_1), and estriol (E_3) [2,3]. The corpus luteum of the ovary is also responsible for the synthesis of progestogens, whose role, via their active form progesterone, is to regulate the female menstrual cycle and pregnancy.

To exert their biological effects, female sex hormones must bind to specific nuclear receptors, such as oestrogen receptors ER-α and ER-β, and progesterone receptors PR-A and PR-B [4].

Article history
Received 30 May 2025 – Accepted 3 Oct 2025

Contact
Umile Giuseppe Longo; g.longo@policlinicocampus.it
Fondazione Policlinico Universitario Campus Bio-Medico, Trigoria, Rome, Italy
Phone: +39 06 225411613

These receptors are expressed in a wide range of tissues, from the endometrium, breast, and ovaries to the vascular smooth muscle, heart, brain, and—relevant to this review—musculoskeletal tissues [5].

Sex hormones and bone

Sex hormones regulate skeletal maturation and homeostasis in both sexes [6]. Oestrogens, progesterone, and androgens play pivotal roles in bone development, sustaining bone health and directly participating in the aging process of bone by modulating bone density, structure, and fracture risk [7].

They exert these functions upon binding to their own receptors, which are expressed in osteoblasts, osteoclasts, osteocytes, and growth plate chondrocytes [8]. Hormone binding activates a cascade of intracellular signalling pathways responsible for the regulation of genes critical for bone resorption, such as RANKL and osteoprotegerin, as well as genes controlling osteoblast differentiation and bone formation, through the Wnt/β-catenin signalling pathway for example [9].

During puberty, sex steroids stimulate bone lengthening mainly through ERα activation in both sexes, in part by boosting the growth hormone–IGF-1 axis (Figure 1) [10]. ERα is also involved in growth plate closure. Beyond growth, sex steroids are critical for maintaining bone strength, as shown by the skeletal changes observed in individuals and animal models with sex hormone deficiencies [11]. Deficiency of sex steroids, by shifting the balance between bone resorption and formation towards overall increased bone mass loss, leads to high bone turnover in both men and women [6].

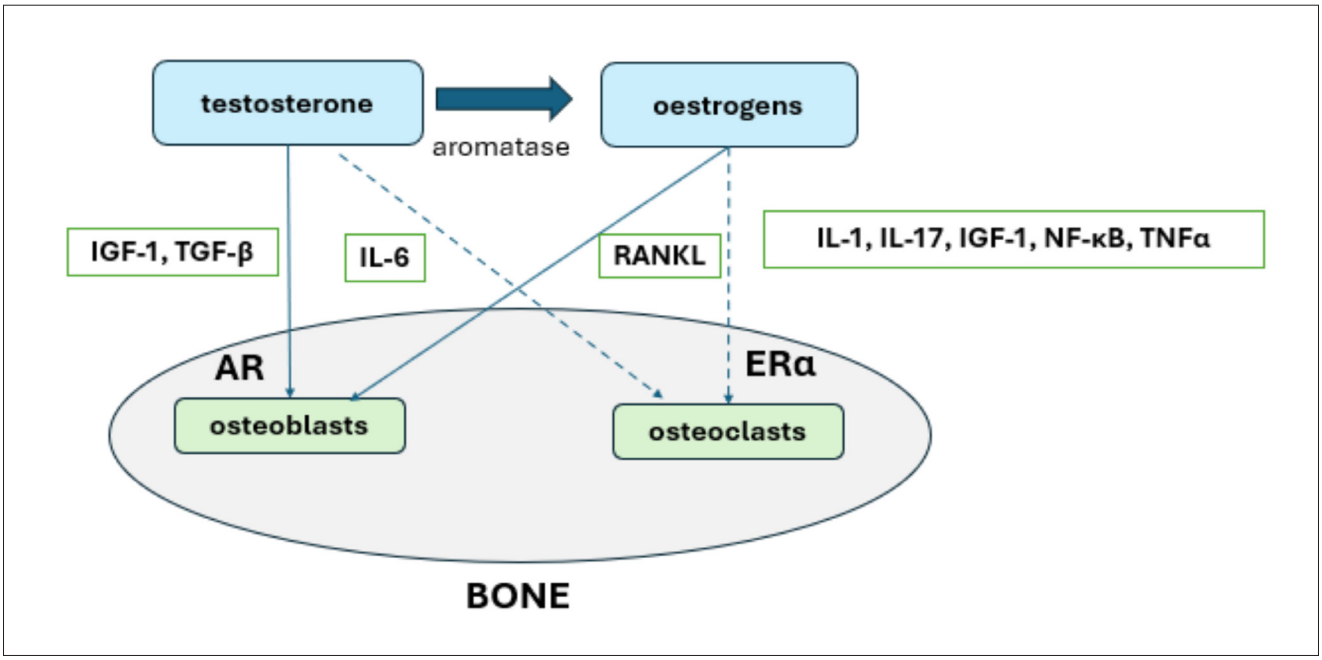
Interestingly, research has shown that oestrogens and androgens reduce the number of bone remodelling cycles by limiting the differentiation of bone precursor cells into osteoclasts and osteoblasts. Furthermore, sex steroids have pro-apoptotic effects on osteoclasts but anti-apoptotic effects on osteoblasts and osteocytes [11]. The loss of these protective effects on mature osteoblasts and osteocytes, combined with increased osteoclast survival, likely shifts the balance towards bone resorption, resulting in progressive bone weakening [12].

Oestrogens

Oestrogens play a complex and sometimes contradictory role in inflammation, acting as both anti-inflammatory and pro-inflammatory agents depending on various factors. Overall, they act as anti-inflammatory agents, especially in bone and vascular tissues, reducing cytokine-mediated inflammation and protecting tissue integrity. However, in autoimmune diseases, oestrogens may enhance inflammatory responses, contributing to disease pathology. This paradoxical action depends on multiple biological and contextual factors, meaning that oestrogens perform a finely tuned immunomodulatory function [13].

Natural oestrogens, particularly E_2, exert potent anti-inflammatory effects through multiple mechanisms. They modulate immune responses by suppressing proinflammatory cytokines such as tumour necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), and by promoting the production of anti-inflammatory cytokines like IL-4, IL-10, and transforming growth factor-beta (TGF-β) [14]. In bone, they reduce inflammation by downregulating proinflammatory pathways, such as NF-κB signalling, and suppressing cytokines, like IL-1, TNF-α, and IL-6, that promote osteoclastogenesis and

Figure 1 Molecular roles of testosterone and oestrogens in bone metabolism. AR, androgen receptor; ERα, oestrogen receptor α; IGF-1, insulin growth factor-1; TGF-β, transforming growth factor-β; IL, interleukin; RANKL, receptor activator of NF-κB ligand; NF-κB, nuclear factor-κB; TNFα, tumour necrotic factor-α. (Reprinted from Shigehara K, Izumi K, Kadono Y, Mizokami A. Testosterone and bone health in men: a narrative review. J Clin Med. Feb 02 2021;10(3) doi:10.3390/jcm10030530).



bone resorption (Figure 1)[10]. This effect is crucial for maintaining bone homeostasis and preventing excessive bone loss, particularly in postmenopausal women in whom oestrogen replacement can mitigate inflammation-driven bone degradation [15].

Conversely, oestrogens can act as pro-inflammatory agents, particularly in some chronic autoimmune diseases like systemic lupus erythematosus and multiple sclerosis. In these contexts, estrogens may enhance B cell activation, alter immune tolerance, and exacerbate autoimmune responses [13]. Namely, the synthetic oestrogen ethinyl estradiol (EE), commonly used in oral contraceptives (OCs), can have proinflammatory effects. While EE exhibits some anti-inflammatory properties, its chemical structure confers higher potency and resistance to metabolic degradation, leading to amplified oestrogenic activity that can stimulate inflammatory pathways. EE has been shown to increase the expression of proinflammatory cytokines and immune activation markers in certain contexts, potentially exacerbating inflammatory reactions [16]. The balance between anti- and proinflammatory effects of EE is complex and depends on dosage, duration of exposure, and individual susceptibility [17].

During puberty, oestrogens are crucial for stimulating longitudinal bone growth and for the closure of the epiphyseal growth plates, allowing females to reach peak bone mass earlier than males, by the end of puberty. Oestrogens further promote endosteal bone apposition, which increases bone density but does not significantly contribute to bone width; this explains why, in early adulthood, women typically have bones of smaller diameter to those of men, but with comparable volumetric mineral density [6].

Oestrogens play a key role in bone homeostasis by balancing bone formation and resorption. Primarily, they suppress osteoclast activity, slowing bone breakdown by inhibiting osteoclast differentiation and promoting osteoclast apoptosis [18]. This anti-resorptive role is mediated through the regulation of genes encoding pro-osteoclastogenic cytokines, such as RANKL (receptor activator of NF-ϰB ligand) and IL-6. Studies in IL-6-deficient mice have shown that bone loss does not occur following ovariectomy, suggesting that IL-6 is involved in mediating the effects of oestrogen on bone [19,20].

Oestrogens support bone formation by enhancing the osteogenic differentiation of mesenchymal stem cells towards the osteoblastic lineage, thus increasing their activity and enhancing collagenic and non-collagenic protein synthesis [21]. They also modulate the Wnt/β-catenin signalling pathway, vital for osteoblast maturation, and reduce sclerostin, a Wnt inhibitor, promoting bone mass accumulation [22]. Furthermore, oestrogens indirectly protect bone by increasing calcium absorption and counteracting the bone-resorbing effects of parathyroid hormone (PTH) [20].

During oestrogen deficiency, such as after menopause, RANKL is overexpressed in bone lining cells and osteocytes, leading to unchecked osteoclast activity, increased bone turnover, trabecular perforation, and osteoporosis (Figure 2) [23]. The positive relationship between oestrogens and bone mass is well established. A woman's total bone mass is closely associated with her oestrogen levels at every stage of life. Between the ages of 25 and 50, there is a gradual decline in bone mass due to aging; however, after menopause, this bone loss accelerates, resulting in a decrease of approximately 10% of total bone mass within five years [24]. Women's dependence on oestrogens for trabecular bone integrity, combined with the dramatic postmenopausal decrease in oestrogens, explains the higher risk of osteoporosis in women compared with men. Over time, men continue to benefit from the dual effects of testosterone: promoting bone formation and maintaining oestrogen levels through peripheral aromatization [22]. The overall risk of fragility fractures throughout life is much higher in women (about 40%) than in men (about 15%), highlighting the protective role of androgens and the greater vulnerability of women to osteoporosis and related fractures [6].

Androgens

Androgens play a key role in stimulating periosteal bone formation, which is responsible for increased bone size and cortical thickness. Furthermore, androgens help maintain bone mass and homeostasis by promoting bone formation and limiting resorption during not only puberty but also adulthood. The direct effects of androgens, as well as their conversion to oestrogens, are important for optimal bone growth and long-term skeletal health in both men and women [25].

There is evidence that testosterone influences bone health both directly, through androgen receptor activation, and indirectly via conversion to estradiol, which exerts estrogenic actions essential for regulating bone turnover [26].

In bone, testosterone is metabolized primarily into two active hormones: dihydrotestosterone (DHT) and estradiol. DHT is produced by 5α-reductase enzymes in osteoblasts and directly stimulates bone formation through androgen receptor signalling, promoting osteoblast activity and inhibiting osteoblast apoptosis. Estradiol, formed via the aromatase enzyme from testosterone, plays a critical role in maintaining bone mineral density (BMD) by inhibiting bone resorption through suppression of osteoclast activity [27].

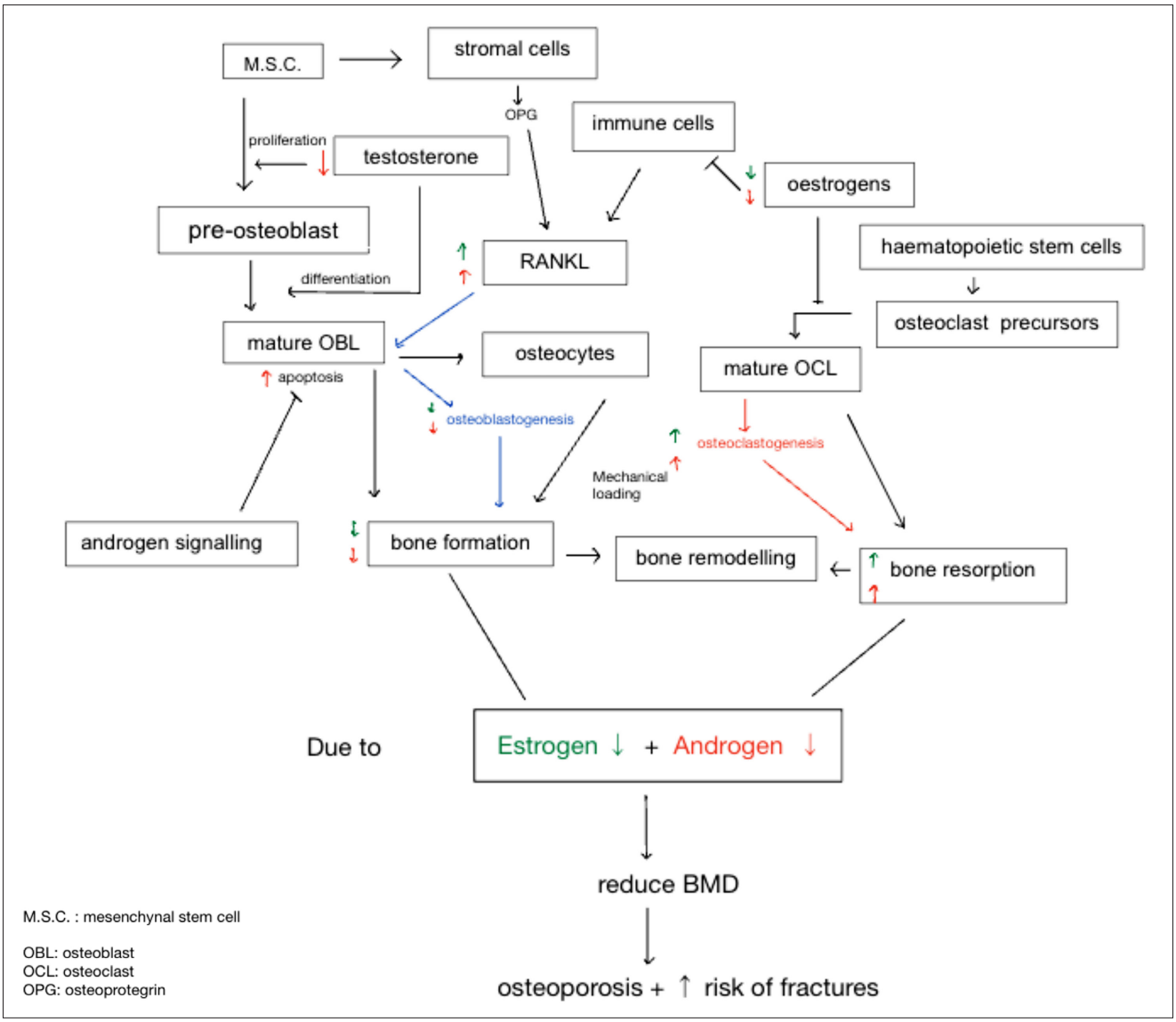
Serum testosterone levels have been positively associated with lumbar BMD up to a certain threshold (~30 ng/dL) in postmenopausal women, suggesting that maintaining adequate testosterone levels may have beneficial effects on bone health. However, high testosterone levels in women can also be linked to adverse conditions such as polycystic ovary syndrome and increased cancer risk [28].

Despite women having lower circulating levels of androgens, these hormones still contribute to bone health, especially after menopause when oestrogen levels drop (Figure 2) [23,29].

Progesterone

The role of progesterone in bone metabolism is less pronounced and less well understood than those of oestrogens and androgens. However, some research suggests that progesterone may work in synergy with oestrogens to promote bone formation and limit bone resorption, especially during the menstrual cycle and pregnancy [30].

Figure 2 A summary of androgen and oestrogen deficiencies in postmenopausal women and the elderly from a cellular and molecular point of view. DHT: dihydrotestosterone; BMD: bone mineral density; RANKL: receptor activator of nuclear factor kappa-B ligand; AR: androgen receptor; M.S.C: mesenchymal stem cell; OBL: osteoblast; OCL: osteoclast; OPG: osteoprotegerin. (Reprinted from Hsu SH, Chen LR, Chen KH. Primary osteoporosis induced by androgen and estrogen deficiency: the molecular and cellular perspective on pathophysiological mechanisms and treatments. Int J Mol Sci. Nov 12 2024;25(22) doi:10.3390/ijms252212139)



Progesterone is thought not only to directly stimulate osteoblasts, increasing bone formation markers like alkaline phosphatase by up to 70%, but also to improve BMD by 1.7% annually, when working synergistically with oestrogen. Women with irregular ovulation have been shown to lose ~1% vertebral BMD annually, highlighting the role of progesterone in maintaining bone mass during the reproductive years [31]. However, the direct effects of progesterone on bone mass and structure are still not entirely clear, and more studies are needed to fully clarify its role in bone health.

Oral contraceptives and bone

The effects of OCs on bone turnover and density are complex and sometimes contradictory. During adolescence, OCs—particularly combined hormonal formulations containing low-dose EE (15-35 mcg)—are associated with reduced bone mineral accumulation, which varies according to oestrogen dose, duration of administration, and use regimen [32]. During the critical years following menarche, users of OCs show smaller gains in BMD, potentially compromising peak bone mass development. Although no evidence of bone loss is reported, spinal and femoral neck BMD gains are significantly lower [33].

In adult premenopausal women, OCs have a neutral-to-positive effect on bone density. Studies in women aged 18–39 show no significant negative impact on BMD, with some showing modest increases or maintenance of bone strength during OC use [34]. These findings suggest that in adults with mature skeletons, OCs do not impair bone density and may help maintain it, especially in women with menstrual irregularities, in whom

OCs can normalize hormone levels [35].

Perimenopausal women tend to exhibit a positive or neutral effect of OCs on bone density. Evidence includes randomized controlled trials and cohort studies showing that long-term OC use (more than 10 years) during perimenopause can stabilize or increase BMD in the lumbar spine, radius, and femoral neck, compared with non-use, which tends to be associated with loss of bone mass. However, some investigations report no significant changes, indicating variability depending on the OC formulation, duration of administration, and individual hormonal milieu [36].

A study by Prior (*Climacteric*, 2018) highlights the importance of precise optimisation of progestin dosage, recommending a tailored approach that considers individual variability in hormone metabolism, receptor responsiveness, and overall health. For younger women using progestin-only contraceptives, higher and continuous doses are often required to suppress ovulation and reliably achieve effective contraception. Conversely, in postmenopausal hormone replacement therapy (HRT), lower progestogen doses are combined with oestrogens mainly to protect the endometrium and relieve symptoms, while aiming to minimise side effects [37]. The progestogen dose in HRT is carefully tailored to the estrogen dose, balancing safety and efficacy [38]. This reflects distinct therapeutic goals of the two applications: contraception requires strong hormonal suppression, while HRT focuses on restoring hormonal balance with few adverse effects. Personalised progestin dosing is essential to optimise benefits and minimise risk across age groups and clinical indications.

Sex hormones and muscle

A growing body of evidence highlights the significant role that sex hormones play throughout life in maintaining muscle homeostasis, mass, strength, and contractile function, as well as metabolic health [39].

Oestrogen and progestogen receptors are present in human skeletal muscle. While androgens and progestogens each act through a single receptor (the androgen receptor [AR] and the progesterone receptor [PR]), multiple oestrogen receptors are expressed within the cytoplasm (ERα and ERβ) and sarcolemma, including the G protein-coupled oestrogen receptor (GPER), oestrogen receptor-X (ER-X), and the Gq-coupled membrane oestrogen receptor (Gq-mER). This difference may be due to evolutionary adaptations [2,40].

While serum concentrations of free testosterone and progesterone influence muscle mass, oestrogens appear to be primarily related to muscular contractile function [2].

Ovarian sex hormones: oestrogens and progesterone

Ovarian sex hormones boost skeletal muscle strength by encouraging the incorporation of strong-binding myosin in muscle fibers [2].

Their role also extends to supporting skeletal muscle regeneration, likely by maintaining the satellite cell pool [2]. This effect is likely achieved through the oestrogen-mediated regulation of myoblast proliferation, and through the differentiation of these cells, in turn modulated by progesterone through its impact on MYOD1 expression [41].

While progesterone sustains muscle mass by promoting muscle protein synthesis, E_2 seems to be more involved in enhancing muscle contractility and force production [42].

Oestrogens

Oestrogens exert both protective and anabolic effects on skeletal muscle. They enhance muscle strength and quality by improving muscle fibre integrity, increasing contractility, and modulating calcium levels in muscle cells to enhance contraction [43]. Oestrogens also reduce muscle damage and inflammation by exerting an antioxidant effect, lowering exercise-induced oxidative stress, and suppressing inflammatory cytokine activity. Additionally, they support muscle repair and recovery by promoting satellite cell activation, crucial for muscle regeneration, and improving blood flow to muscle tissue [44,45].

During exercise, oestrogens promote metabolic efficacy by enhancing mitochondrial bioenergetics, boosting ATP production while increasing glucose uptake in skeletal muscle via both insulin-dependent and -independent pathways [46].

Oestrogen deficiency accelerates age-related muscle loss, increases intramuscular fat deposition, and impairs mitochondrial bioenergetics, leading to reduced oxidative metabolism and energy production [2]. As Phillips *et al*. demonstrated, women post menopause experience earlier and greater losses of muscle strength than men of similar age, but oestrogen-based hormone therapy can help preserve muscle strength [47]. Evidence from both human and animal studies indicates that oestrogens primarily improve the intrinsic quality of muscle, enhancing its ability to generate force, rather than simply increasing muscle mass as androgens do.[46] After menopause, declining oestrogen levels contribute to loss of muscle mass (sarcopenia) and strength, increasing fall and fracture risk [48].

Progesterone

Progesterone contributes to muscle homeostasis largely by acting synergistically with oestrogens and androgens. While it does not directly increase muscle mass, progesterone contributes to muscle protein synthesis and modulates metabolic processes, including energy utilisation and endurance capacity [42]. In fact, progesterone modulates the metabolic effects of oestrogens: when combined with oestrogens, progesterone reverses glycogen sparing in muscle, restoring carbohydrate oxidation to baseline levels during exercise [49]. This highlights that progesterone's role in muscle metabolism is context-dependent, balancing oestrogen-driven energy regulation rather than independently promoting muscle anabolism [42].

By acting on the nervous system, progesterone indirectly affects muscle tone, potentially influencing neuromuscular coordination. While not directly increasing muscle mass or

strength on its own, it works synergistically with testosterone to stimulate muscle protein synthesis in women after menopause [42].

Androgens

Androgens, particularly testosterone, are powerful regulators of muscle hypertrophy and strength. They promote muscle protein synthesis by activating AR signalling, which in turn stimulates pathways such as IGF-1 and the mTOR/Akt cascade, while also inhibiting myostatin, a key negative regulator of muscle growth [50]. Testosterone further enhances mitochondrial function and oxidative capacity, supporting efficient muscle energy metabolism [51].

Testosterone levels are much lower in women than in men, typically ranging from 0.4 to 2.0 nmol/L compared with 8.8–30.9 nmol/L [52]. Although total testosterone is not consistently linked to muscle strength in women, its bioavailable (free) fraction correlates positively with lean body mass both before and after menopause, indicating an anabolic effect that helps maintain muscle size [2].

Androgens also improve muscle quality by increasing fibre size and contractile force, particularly in type II (fast-twitch) fibres [51]. In young women, even modest increases in testosterone can lead to type II fibre hypertrophy and increased capillarisation, which may enhance muscle performance and endurance [53]. However, muscle strength is not solely determined by physiological testosterone levels; rather, it is influenced by a combination of sex hormones and other factors [2].

In summary, while oestrogens support muscle repair and metabolic flexibility, and progesterone modulates energy substrate utilisation, androgens directly drive muscle mass and strength gains. The interplay of these hormones underscores the complexity of hormonal regulation in skeletal muscle health.

Female sex hormones and tendons

Tendons, as vital structures connecting muscle to bone, play a central role in force transmission and coordinated movement. Recent research has highlighted the influence of female sex hormones—particularly oestrogens—on tendon structure and function [54].

Significant sex differences have been identified in tendon composition and mechanical characteristics, and genetic factors such as *COL5A1* polymorphisms have been investigated. While demonstrating no association with rotator cuff tears, research on the *COL5A1* gene highlights the multifactorial nature of tendon vulnerability and suggests that regulatory factors, such as sex hormones, may play a more prominent role in modulating tendon properties [55].

In general, women tend to have lower tendon dry mass relative to wet weight and reduced collagen content, which results in decreased stiffness. These variations are largely influenced by hormonal activity, most notably the effects of oestrogens. Oestrogens appear to inhibit the synthesis of key structural proteins, like collagen, and suppress the activity of lysyl oxidase, an enzyme critical for forming strong collagen cross-links. Conversely, androgens, such as DHT, may exert anabolic effects on tendon cells, as DHT has been shown to stimulate proliferation and collagen expression in cultured human tenocytes, highlighting the divergent effects of sex hormones on tendon metabolism [56]. As a result, tendons in women may be more compliant and prone to elongation or deformation when subjected to stress [57].

Examination of collagen synthesis in tendons shows that women consistently exhibit lower rates than men, both at rest and after exercise. Oestrogens seem to attenuate the tendon's anabolic response to mechanical loading, thereby limiting its capacity to remodel and strengthen following physical training. This phenomenon is especially important in female athletes and active individuals, in whom effective tendon adaptation is essential for injury prevention and performance.

In women using OCs, the hormonal milieu also influences tendon metabolism. OCs often lower circulating levels of insulin-like growth factor I, a powerful promoter of collagen synthesis, and their use may therefore further reduce tendon collagen synthesis [58].

In post-menopause, HRT appears to have a distinct impact. Supplementation under low baseline hormonal conditions can enhance collagen production in tendons. However, this increase in metabolic activity does not necessarily result in improved mechanical properties. In fact, some studies suggest that tendon stiffness may decline despite higher collagen synthesis, potentially due to disrupted collagen cross-linking.

Oestrogen levels are known to decline dramatically after menopause, which seems to equalize the risk of Achilles tendon rupture between the sexes. Similarly, the use of OCs, which maintain moderate oestrogen levels, has been linked to an increased risk of Achilles tendinopathy [59]. This raises the possibility that physiological cyclical oestrogen surges may play a protective role in tendon health—a role which steady-state levels do not seem to replicate.

Taken together, these findings underscore the complex and context-dependent role of oestrogen in tendon physiology. While high oestrogen levels in younger women may reduce tendon resilience and adaptability, moderate supplementation in postmenopausal women may offer metabolic benefits, albeit without restoring biomechanical strength.

Female sex hormones and ligaments

Ligaments, which connect bone to bone and are essential for joint stability, are also influenced by fluctuations in female sex hormones—particularly oestrogens and progesterone. A growing body of evidence suggests that oestrogens have a predominantly negative effect on the mechanical properties of ligaments. Specifically, they can reduce both the strength and the stiffness of ligament tissue by interfering with collagen turnover and impairing the cross-linking mechanisms necessary for the formation of durable, load-bearing connective tissue. Animal studies have further substantiated this effect, showing that high oestrogen levels can diminish the load-bearing capacity of key ligaments, such as the anterior cruciate ligament (ACL) [59].

Hormonal fluctuations throughout the menstrual cycle can further modulate ligament behaviour. During the late follicular phase, when oestrogen levels peak and progesterone remains low, women commonly exhibit increased joint laxity, particularly of the knee. This transient laxity is believed to stem from the impact of oestrogens on the ligament's extracellular matrix and collagen organisation. The resulting changes in joint stability may help explain the observed rise in ACL injury rates during this phase of the cycle [60].

The role of progesterone is less well defined but may have a moderating influence on the effects of oestrogen. The combined hormonal shifts that occur across the menstrual cycle result in dynamic variations in ligament stiffness and neuromuscular control, which may increase injury susceptibility at specific times of the cycle [61].

Oral contraceptives may help buffer these fluctuations by maintaining more consistent hormone levels. Some studies suggest that OCs reduce joint laxity and may lower injury risk by stabilising ligament properties. However, the literature remains inconclusive, with some research reporting negligible effects [62].

In summary, oestrogens tend to reduce ligament stiffness and mechanical strength by disrupting collagen homeostasis. These effects, particularly pronounced during phases of the menstrual cycle characterised by elevated oestrogen levels, contribute to the higher incidence of ligamentous injuries—especially ACL ruptures—observed in female athletes.

Female sex hormones and cartilage

Sex hormones maintain cartilage health, and alterations in their levels may thus influence the development of degenerative joint conditions. Chondrocytes—the principal cells within articular cartilage—express receptors for several sex hormones, including oestrogens (ERs) and androgens (ARs), enabling them to directly respond to hormonal cues [63].

Among these hormones, oestrogens—particularly E_2—have been shown to exert a protective effect on cartilage tissue. They promote the synthesis of extracellular matrix components such as collagen and proteoglycans, while simultaneously inhibiting matrix-degrading enzymes, including matrix metalloproteinases. In this way, oestrogens help preserve the structural and functional integrity of articular cartilage. Additionally, they can downregulate inflammatory mediators within the joint, thereby reducing the catabolic effects of cytokines that drive cartilage degradation in inflammatory or osteoarthritic environments [64].

Androgens also influence cartilage, primarily through their interaction with ARs on chondrocytes. These interactions may enhance cell proliferation and matrix production, although the effects can vary depending on the hormonal milieu and local tissue context. Notably, the presence of both ARs and ERs in chondrocytes suggests a nuanced interplay between these hormones in regulating cartilage homeostasis [65,66].

Aromatase, expressed in chondrocytes, locally converts androgens into oestrogens within cartilage, serving as an important regulatory factor. This suggests that chondrocytes may exert autocrine or paracrine control over their hormonal environment. Inhibition of aromatase can disrupt this mechanism, leading to decreased local oestrogen levels and potentially compromising cartilage integrity [67].

Beyond direct receptor-mediated effects, sex hormones influence gene expression patterns within chondrocytes, upregulating anabolic genes involved in matrix synthesis while suppressing catabolic genes responsible for degradation. This hormonal regulation is particularly important during periods of endocrine transition, such as menopause, when declining oestrogen levels may accelerate cartilage breakdown and contribute to the development of osteoarthritis [68].

In conclusion, sex hormones—particularly oestrogens—are key regulators of cartilage metabolism. By modulating chondrocyte function, matrix turnover, and inflammatory signalling, they play a central role in maintaining cartilage health and may offer therapeutic targets in the management of degenerative joint diseases.

Hormonal fluctuations and injury risk in female athletes

The menstrual cycle has a profound influence on musculoskeletal function in female athletes, largely due to cyclical fluctuations in sex steroid hormones—primarily oestrogens and progesterone, with relaxin also playing a potential contributory role [69].

The cycle is typically divided into three phases: the follicular phase, ovulation, and the luteal phase. Oestrogen levels rise progressively during the follicular phase and peak at ovulation, while progesterone levels are lowest in the follicular phase and increase significantly during the luteal phase [70]. These hormonal variations directly affect the mechanical properties of connective tissues, neuromuscular coordination, and injury susceptibility.

Elevated oestrogen levels, particularly during the peri-ovulatory period, have been associated with increased ligamentous laxity. This effect is thought to occur through oestrogen-mediated suppression of the activity of lysyl oxidase [57]. As a result, soft tissues may become more compliant and less able to resist tensile forces, increasing the likelihood of sprains and ruptures.

Oestrogens also appear to influence neuromuscular control. For instance, they may modulate muscle activation patterns and joint stabilisation strategies, potentially impairing coordination at critical moments. Some notable studies demonstrated that ACL injury rates in female athletes are significantly higher during the ovulatory phase, a period marked by peak oestradiol levels and increased knee joint laxity [71].

Relaxin, although primarily associated with pregnancy, is also present during the luteal phase, and may synergistically contribute to ligamentous relaxation. Human studies on the role of relaxin in athletic injury risk have shown mixed results, but the hormone's capacity to reduce tissue stiffness remains a plausible contributor to injury vulnerability [72,73].

Beyond ligaments, neuromuscular changes linked to hormonal fluctuations may also increase the risk of non-ligamentous injuries. Increased postural sway and decreased proprioception have been reported during the ovulatory phase, which

may predispose athletes to ankle sprains, muscle strains, and falls. Moreover, hormone-driven changes in tendon stiffness and force transmission may contribute to overuse injuries such as patellofemoral pain syndrome [74].

Taken together, the hormonal shifts that occur throughout the menstrual cycle represent a significant, yet often overlooked, injury risk factor for female athletes. Addressing these physiological changes is essential for optimising training and injury prevention strategies in women's sports.

ACL injury risk in female athletes

Anterior cruciate ligament injuries are among the most severe and debilitating injuries in sport, and occur disproportionately in female athletes. The ACL is a key stabiliser of the knee, particularly for rotational and anterior-posterior motion. Most ACL injuries in sport result from non-contact mechanisms, such as sudden deceleration, pivoting, or landing awkwardly from a jump—movements that are common in sports like football (soccer), basketball, and handball [75,76].

Female athletes face a substantially greater risk of ACL rupture compared with their male counterparts, due to a combination of biomechanical, anatomical, neuromuscular, and hormonal factors [76]. Importantly, ACL injuries often carry long-term consequences: high re-injury rates, persistent functional limitations, and an increased risk of early-onset osteoarthritis [77].

Many of these injuries occur during actions that lead to poor trunk stability, excessive knee valgus, and limited hip control—issues often linked to neuromuscular imbalances that develop during adolescence [78]. After ACL reconstruction, women tend to return to sport more slowly than men and often report lower confidence and satisfaction with their knee function [79]. Unfortunately, if these injuries occur during critical periods of athletic development, such as adolescence or early adulthood, they may derail an athlete's career and carry significant psychosocial implications.

Given the complexity and long-term impact of ACL injuries, especially in women, it is essential to consider them as a distinct clinical challenge requiring sex-specific risk assessment, preventive approaches, and rehabilitation strategies.

Epidemiology of ACL injury risk in female athletes

Epidemiological data consistently show the greater risk of ACL injury in females versus males, particularly during adolescence. Girls aged 15 to 19 represent the highest risk group, with studies reporting that females have a 2 to 8 times greater chance of sustaining an ACL tear in high-demand sports such as soccer, basketball, and skiing [80]. In some settings, the female-to-male injury ratio is as high as 9:1, particularly at amateur and recreational levels, where access to proper injury prevention programmes is often limited [81].

Longitudinal research in elite female athletes, such as Norwegian football players, has shown that ACL injuries are not only the most common serious knee injuries but also the ones associated with the longest recovery times—typically requiring 6 to 12 months of rehabilitation [81].

Moreover, recurrence rates are notably high. Approximately 30–40% of elite female footballers experience a second ACL rupture—affecting either the same or the contralateral knee—compared with 20% in male athletes [82]. Factors contributing to these recurrence rates include inadequate rehabilitation, premature return to sport, and persistent modifiable risk factors.

Additional epidemiological concerns have been raised over athletes with irregular menstrual cycles, poor nutritional intake, or conditions like Relative Energy Deficiency in Sport (RED-S), who appear to be at even higher risk. These conditions disrupt normal hormonal function and contribute to impaired tissue repair, increased fatigue, and delayed recovery [83].

Contributing factors to ACL injury risk in female athletes

The increased risk of ACL injuries in female athletes arises from a multifaceted interplay of intrinsic and extrinsic factors. On a biomechanical level, women tend to exhibit increased dynamic knee valgus, greater quadriceps dominance, and reduced hamstring recruitment during high-impact movements. These patterns result in elevated anterior tibial shear forces, which increase strain on the ACL [78].

Neuromuscular imbalances, particularly if not addressed through structured training during adolescence, further compound this vulnerability. Females often demonstrate delayed or altered muscle activation patterns that compromise knee joint stability during dynamic activities [84].

Anatomical differences also contribute to risk. Females generally have a narrower intercondylar notch, a smaller ACL cross-sectional area, and a greater Q-angle at the knee [85]. These structural characteristics may reduce the mechanical threshold needed for ligament rupture to occur [86].

Hormonal influences are equally important. Elevated oestrogen levels, especially during certain menstrual phases, can increase ligament laxity and reduce neuromuscular efficiency. While the roles of progesterone and relaxin are less well defined, both hormones may contribute to increased soft tissue compliance, particularly in the luteal phase [87,88].

Extrinsic factors further influence injury risk. Poor-quality playing surfaces, lack of access to sex-specific coaching, and nutritional imbalances—particularly linked to low energy availability—exacerbate vulnerability. RED-S, a condition characterised by inadequate caloric intake relative to energy expenditure, has been linked to impaired bone health, disrupted menstrual cycles, and greater injury risk [89].

Given this complex landscape, ACL injury prevention in female athletes must be approached from a comprehensive, sex-specific perspective that integrates biomechanical training, hormonal education, nutritional support, and individualised rehabilitation.

Injury prevention in female athletes

Given their heightened vulnerability to injuries such as ACL tears, injury prevention is a key priority for female athletes.

Multicomponent exercise-based programmes are the most

effective strategies, as they address both intrinsic and extrinsic risk factors. Neuromuscular training programmes, including FIFA 11+ and PEP, are key examples of such strategies. According to evidence in systematic reviews and meta-analyses, these programmes, when applied to female football players, reduce overall injury rates by 27% and ACL injury rates by up to 45% [90,91]. Some studies indicate that when they are well implemented, the risk of ACL injury can be reduced by as much as 90% [76].

Key components of successful injury prevention programmes include plyometric exercises, strength training for the lower body and core, and exercises for balance, proprioception, agility, and neuromuscular control. Training programmes should be adjusted to suit the physiological and biological features of each female athlete**,** particularly taking into account menstrual cycle phases and hormonal profiles, which influence ligament laxity and neuromuscular control [91]. For example, the FIFA 11+ program, which combines warm-up, strength, plyometric, and balance exercises, has been shown to reduce overall injury rates by 34%, lower limb injuries by 29%, and head/neck injuries by 40% [91].

Lack of adequate medical support, player motivation, and coach engagement may undermine the effectiveness of these programmes. Over 80% of elite female athletes report undertaking injury prevention exercises at their clubs, with two-thirds using the FIFA 11+ programme [92]. However, inconsistent implementation and lack of follow-up can reduce the impact of these interventions [91].

In young women, hormonal cycling should be managed in accordance with the specific training demands. Monitoring hormonal cycles and modulating them through the use of OCs has emerged as a promising strategy to reduce injury risk in female athletes [62]. Recent data indicate that OCs may exert a protective effect against ACL tears, with the most pronounced benefit reported in younger athletes: among females aged 15–19, administration of OCs resulted in a 63% reduction in the rate of ACL tears (odds ratio 0.37, 95% CI 0.27–0.50) [62]. Across all ages, OC users experienced a modest but significant reduction in ACL reconstruction rates (0.56% vs 0.69% in non-users, $p < 0.001$) [62].

Hormonal modulation with OCs stabilizes the menstrual cycle, dampening the natural fluctuations in oestrogen and progesterone levels that contribute to increased ligament laxity and neuromuscular inefficiency at certain cycle phases. This stabilisation may mitigate the heightened risk of injury observed during the late luteal and early follicular phases, when injury incidence rates are elevated. While the effects of OCs on bone density and on other soft tissue injuries remain less clear, and individual responses vary, current evidence suggests that OCs should be considered for injury prevention in high-risk populations, provided they are prescribed judiciously and tailored to the athlete's health profile [62,93,94].

In summary, the main strategies for injury prevention in female athletes are multicomponent, exercise-based programmes that target neuromuscular training, strength, and balance. These programmes, when consistently implemented, can reduce overall and ACL injury risk by 27–45% or more, with the greatest benefits observed in programmes designed specifically to meet the unique requirements of the female athlete [95].

Lastly, tracking hormonal cycles and modulating them through the use of OCs can substantially lower the risk of ACL injury in female athletes, especially adolescents, and should be considered as part of a comprehensive injury prevention strategy.

References

1. Longo UG, Mazzola A, Carotti S, et al. The role of estrogen and progesterone receptors in the rotator cuff disease: a retrospective cohort study. BMC Musculoskelet Disord. 2021;22(1):891.
2. Alexander SE, Pollock AC, Lamon S. The effect of sex hormones on skeletal muscle adaptation in females. Eur J Sport Sci. 2022;22(7):1035-45.
3. Cui J, Shen Y, Li R. Estrogen synthesis and signaling pathways during aging: from periphery to brain. Trends Mol Med. 2013;19(3):197-209.
4. Ellmann S, Sticht H, Thiel F, Beckmann MW, Strick R, Strissel PL. Estrogen and progesterone receptors: from molecular structures to clinical targets. Cell Mol Life Sci. A2009;66(15):2405-26.
5. Ekenros L, Papoutsi Z, Fridén C, Dahlman Wright K, Lindén Hirschberg A. Expression of sex steroid hormone receptors in human skeletal muscle during the menstrual cycle. Acta Physiol (Oxf). 2017;219(2):486-93.
6. Venken K, Callewaert F, Boonen S, Vanderschueren D. Sex hormones, their receptors and bone health. Osteoporos Int. 2008;19(11):1517-25.
7. Szulc P. Role of sex steroids hormones in the regulation of bone metabolism in men: evidence from clinical studies. Best Pract Res Clin Endocrinol Metab. 2022;36(2):101624.
8. Syed F, Khosla S. Mechanisms of sex steroid effects on bone. Biochem Biophys Res Commun. 2005;328(3):688-96.
9. Kostenuik PJ. Osteoprotegerin and RANKL regulate bone resorption, density, geometry and strength. Curr Opin Pharmacol. 2005;5(6):618-25.
10. Shigehara K, Izumi K, Kadono Y, Mizokami A. Testosterone and bone health in men: a narrative review. J Clin Med. 2021;10(3):530.
11. Manolagas SC, Kousteni S, Jilka RL. Sex steroids and bone. Recent Prog Horm Res. 2002;57:385-409.
12. Bellido T. Osteocyte-driven bone remodeling. Calcif Tissue Int. 2014;94(1):25-34.
13. Straub RH. The complex role of estrogens in inflammation. Endocr Rev. 2007;28(5):521-74.
14. Shivers KY, Amador N, Abrams L, Hunter D, Jenab S, Quiñones-Jenab V. Estrogen alters baseline and inflammatory-induced cytokine levels independent from hypothalamic-pituitary-adrenal axis activity. Cytokine. 2015;72(2):121-9.
15. Ghisletti S, Meda C, Maggi A, Vegeto E. 17beta-estradiol inhibits inflammatory gene expression by controlling NF-kappaB intracellular localization. Mol Cell Biol. 2005;25(8):2957-68.
16. Subramanian S, Matejuk A, Zamora A, Vandenbark AA, Offner H. Oral feeding with ethinyl estradiol suppresses and treats experimental autoimmune encephalomyelitis in SJL mice and inhibits the recruitment of inflammatory cells into the central nervous system. J Immunol. 2003;170(3):1548-55.
17. Dai R, Edwards MR, Heid B, Ahmed SA. 17β-estradiol and 17α-ethinyl estradiol exhibit immunologic and epigenetic regulatory effects in NZB/WF1 female mice. Endocrinology. 2019;160(1):101-18.
18. Shiau HJ, Aichelmann-Reidy ME, Reynolds MA. Influence of sex steroids on inflammation and bone metabolism. Periodontol 2000. 2014;64(1):81-94.
19. Poli V, Balena R, Fattori E, et al. Interleukin-6 deficient mice are protected from bone loss caused by estrogen depletion. EMBO

J.1994;13(5):1189-96.
20. Väänänen HK, Härkönen PL. Estrogen and bone metabolism. Maturitas. 1996;23 Suppl:S65-9.
21. Okazaki R, Inoue D, Shibata M, et al. Estrogen promotes early osteoblast differentiation and inhibits adipocyte differentiation in mouse bone marrow stromal cell lines that express estrogen receptor (ER) alpha or beta. Endocrinology. 2002;143(6):2349-56.
22. Emmanuelle NE, Marie-Cécile V, Florence T, et al. Critical role of estrogens on bone homeostasis in both male and female: from physiology to medical implications. Int J Mol Sci. 2021;22(4):1568.
23. Hsu SH, Chen LR, Chen KH. Primary osteoporosis induced by androgen and estrogen deficiency: the molecular and cellular perspective on pathophysiological mechanisms and treatments. Int J Mol Sci. 2024;25(22):12139.
24. Brown M. Skeletal muscle and bone: effect of sex steroids and aging. Adv Physiol Educ. 2008;32(2):120-6.
25. Vanderschueren D, Vandenput L, Boonen S, Lindberg MK, Bouillon R, Ohlsson C. Androgens and bone. Endocr Rev. 2004;25(3):389-425.
26. Mohamad NV, Soelaiman IN, Chin KY. A concise review of testosterone and bone health. Clin Interv Aging. 2016;11:1317-24.
27. Stephens-Shields AJ, Snyder PJ, Ellenberg SS, Taylor L, Bhasin S. Relation of testosterone, dihydrotestosterone, and estradiol with changes in outcomes measures in the testosterone trials. J Clin Endocrinol Metab. 2022;107(5):1257-69.
28. Yang J, Kong G, Yao X, Zhu Z. Association between serum total testosterone level and bone mineral density in middle-aged postmenopausal women. Int J Endocrinol. 2022;2022:4228740.
29. Tok EC, Ertunc D, Oz U, Camdeviren H, Ozdemir G, Dilek S. The effect of circulating androgens on bone mineral density in postmenopausal women. Maturitas. 2004;48(3):235-42.
30. Prior JC. Progesterone as a bone-trophic hormone. Endocr Rev. 1990;11(2):386-98.
31. Seifert-Klauss V, Schmidmayr M, Hobmaier E, Wimmer T. Progesterone and bone: a closer link than previously realized. Climacteric. 2012;15 Suppl 1:26-31.
32. Ampatzis C, Zervoudis S, Iatrakis G, Mastorakos G. Effect of oral contraceptives on bone mineral density. Acta Endocrinol (Buchar). 2022;18(3):355-60.
33. Orsolini LR, Goldberg TBL, Caldeirão TD, et al. Bone impact after two years of low-dose oral contraceptive use during adolescence. PLoS One. 2023;18(6):e0285885.
34. Prior JC, Kirkland SA, Joseph L, et al. Oral contraceptive use and bone mineral density in premenopausal women: cross-sectional, population-based data from the Canadian Multicentre Osteoporosis Study. CMAJ. 2001;165(8):1023-9.
35. Scholes D, Ichikawa L, LaCroix AZ, et al. Oral contraceptive use and bone density in adolescent and young adult women. Contraception. 2010;81(1):35-40.
36. Liu SL, Lebrun CM. Effect of oral contraceptives and hormone replacement therapy on bone mineral density in premenopausal and perimenopausal women: a systematic review. Br J Sports Med. 2006;40(1):11-24.
37. Prior JC. Progesterone for the prevention and treatment of osteoporosis in women. Climacteric. 2018;21(4):366-74.
38. García-Sáenz M, Ibarra-Salce R, Pozos-Varela FJ, et al. Understanding progestins: from basics to clinical applicability. J Clin Med. 2023;12(10):3388
39. Emmert ME, Emmert AS, Goh Q, Cornwall R. Sexual dimorphisms in skeletal muscle: current concepts and research horizons. J Appl Physiol (1985). 2024;137(2):274-99.
40. Yoh K, Ikeda K, Horie K, Inoue S. Roles of estrogen, estrogen receptors, and estrogen-related receptors in skeletal muscle: regulation of mitochondrial function. Int J Mol Sci. 2023;24(3):1853.
41. Collins BC, Arpke RW, Larson AA, et al. Estrogen regulates the satellite cell compartment in females. Cell Rep. 2019;28(2):368-381.e6.
42. Smith GI, Yoshino J, Reeds DN, et al. Testosterone and progesterone, but not estradiol, stimulate muscle protein synthesis in postmenopausal women. J Clin Endocrinol Metab. 2014;99(1):256-65.
43. Pellegrino A, Tiidus PM, Vandenboom R. Mechanisms of estrogen influence on skeletal muscle: mass, regeneration, and mitochondrial function. Sports Med. 2022;52(12):2853-69.
44. Kendall B, Eston R. Exercise-induced muscle damage and the potential protective role of estrogen. Sports Med. 2002;32(2):103-23.
45. Tiidus PM, Lowe DA, Brown M. Estrogen replacement and skeletal muscle: mechanisms and population health. J Appl Physiol (1985). 2013;115(5):569-78.
46. Spangenburg EE, Geiger PC, Leinwand LA, Lowe DA. Regulation of physiological and metabolic function of muscle by female sex steroids. Med Sci Sports Exerc. 2012;44(9):1653-62.
47. Phillips SK, Rook KM, Siddle NC, Bruce SA, Woledge RC. Muscle weakness in women occurs at an earlier age than in men, but strength is preserved by hormone replacement therapy. Clin Sci (Lond). 1993;84(1):95-8.
48. Messier V, Rabasa-Lhoret R, Barbat-Artigas S, Elisha B, Karelis AD, Aubertin-Leheudre M. Menopause and sarcopenia: a potential role for sex hormones. Maturitas. 2011;68(4):331-6.
49. D'Eon TM, Sharoff C, Chipkin SR, Grow D, Ruby BC, Braun B. Regulation of exercise carbohydrate metabolism by estrogen and progesterone in women. Am J Physiol Endocrinol Metab. 2002;283(5):E1046-55.
50. Notelovitz M. Androgen effects on bone and muscle. Fertil Steril. 2002;77 Suppl 4:S34-41.
51. Dubois V, Laurent M, Boonen S, Vanderschueren D, Claessens F. Androgens and skeletal muscle: cellular and molecular action mechanisms underlying the anabolic actions. Cell Mol Life Sci. 2012;69(10):1651-67.
52. Clark RV, Wald JA, Swerdloff RS, et al. Large divergence in testosterone concentrations between men and women: frame of reference for elite athletes in sex-specific competition in sports, a narrative review. Clin Endocrinol (Oxf). 2019;90(1):15-22.
53. Horwath O, Apró W, Moberg M, et al. Fiber type-specific hypertrophy and increased capillarization in skeletal muscle following testosterone administration in young women. J Appl Physiol (1985). 2020;128(5):1240-50.
54. Hansen M. Female hormones: do they influence muscle and tendon protein metabolism? Proc Nutr Soc. 2018;77(1):32-41.
55. Longo UG, Margiotti K, Petrillo S, et al. Genetics of rotator cuff tears: no association of col5a1 gene in a case-control study. BMC Med Genet. 2018;19(1):217.
56. Denaro V, Ruzzini L, Longo UG, et al. Effect of dihydrotestosterone on cultured human tenocytes from intact supraspinatus tendon. Knee Surg Sports Traumatol Arthrosc. 2010;18(7):971-6.
57. Lee CA, Lee-Barthel A, Marquino L, Sandoval N, Marcotte GR, Baar K. Estrogen inhibits lysyl oxidase and decreases mechanical function in engineered ligaments. J Appl Physiol (1985). 2015;118(10):1250-7.
58. Hansen M, Miller BF, Holm L, et al. Effect of administration of oral contraceptives in vivo on collagen synthesis in tendon and muscle connective tissue in young women. J Appl Physiol (1985). 2009;106(4):1435-43.
59. Holmes GB, Lin J. Etiologic factors associated with symptomatic Achilles tendinopathy. Foot Ankle Int. 2006;27(11):952-9.
60. Heitz NA, Eisenman PA, Beck CL, Walker JA. Hormonal changes throughout the menstrual cycle and increased anterior cruciate ligament laxity in females. J Athl Train. 1999;34(2):144-9.
61. Romani W, Patrie J, Curl LA, Flaws JA. The correlations between estradiol, estrone, estriol, progesterone, and sex hormone-binding globulin and anterior cruciate ligament stiffness in healthy, active females. J Womens Health (Larchmt). 2003;12(3):287-98.
62. DeFroda SF, Bokshan SL, Worobey S, Ready L, Daniels AH, Owens BD. Oral contraceptives provide protection against anterior cruciate

ligament tears: a national database study of 165,748 female patients. Phys Sportsmed. 2019;47(4):416-20.
63. Claassen H, Schicht M, Brandt J, et al. C-28/I2 and T/C-28a2 chondrocytes as well as human primary articular chondrocytes express sex hormone and insulin receptors—useful cells in study of cartilage metabolism. Ann Anat. 2011;193(1):23-9.
64. Claassen H, Steffen R, Hassenpflug J, et al. 17β-estradiol reduces expression of MMP-1, -3, and -13 in human primary articular chondrocytes from female patients cultured in a three dimensional alginate system. Cell Tissue Res. 2010;342(2):283-93.
65. Hui L, Shoumei X, Zhoujing Z, et al. Effects of androgen receptor overexpression on chondrogenic ability of rabbit articular chondrocytes. Tissue Eng Regen Med. 2021;18(4):641-50.
66. Nasatzky E, Schwartz Z, Soskolne WA, et al. Evidence for receptors specific for 17 beta-estradiol and testosterone in chondrocyte cultures. Connect Tissue Res. 1994;30(4):277-94.
67. Schicht M, Ernst J, Nielitz A, et al. Articular cartilage chondrocytes express aromatase and use enzymes involved in estrogen metabolism. Arthritis Res Ther. 2014;16(2):R93.
68. Koelling S, Miosge N. Sex differences of chondrogenic progenitor cells in late stages of osteoarthritis. Arthritis Rheum. 2010;62(4):1077-87.
69. Weidauer L, Zwart MB, Clapper J, Albert J, Vukovich M, Specker B. Neuromuscular performance changes throughout the menstrual cycle in physically active females. J Musculoskelet Neuronal Interact. 2020;20(3):314-24.
70. Owen JA Jr. Physiology of the menstrual cycle. Am J Clin Nutr. 1975;28(4):333-8.
71. Wojtys EM, Huston LJ, Boynton MD, Spindler KP, Lindenfeld TN. The effect of the menstrual cycle on anterior cruciate ligament injuries in women as determined by hormone levels. Am J Sports Med. 2002;30(2):182-8.
72. Belanger L, Burt D, Callaghan J, Clifton S, Gleberzon BJ. Anterior cruciate ligament laxity related to the menstrual cycle: an updated systematic review of the literature. J Can Chiropr Assoc. 2013;57(1):76-86.
73. Berger GK, Rockov ZA, Byrne C, Trentacosta NE, Stone MA. The role of relaxin in anterior cruciate ligament injuries: a systematic review. Eur J Orthop Surg Traumatol. 2023;33(8):3319-26.
74. Martínez-Fortuny N, Alonso-Calvete A, Da Cuña-Carrera I, Abalo-Núñez R. Menstrual cycle and sport injuries: a systematic review. Int J Environ Res Public Health. 2023;20(4):3264.
75. Toth AP, Cordasco FA. Anterior cruciate ligament injuries in the female athlete. J Gend Specif Med. 2001;4(4):25-34.
76. Mancino F, Kayani B, Gabr A, Fontalis A, Plastow R, Haddad FS. Anterior cruciate ligament injuries in female athletes: risk factors and strategies for prevention. Bone Jt Open. 2024;5(2):94-100.
77. Lohmander LS, Ostenberg A, Englund M, Roos H. High prevalence of knee osteoarthritis, pain, and functional limitations in female soccer players twelve years after anterior cruciate ligament injury. Arthritis Rheum. 2004;50(10):3145-52.
78. Hewett TE, Myer GD, Ford KR, et al. Biomechanical measures of neuromuscular control and valgus loading of the knee predict anterior cruciate ligament injury risk in female athletes: a prospective study. Am J Sports Med. 2005;33(4):492-501.
79. Ardern CL, Österberg A, Tagesson S, Gauffin H, Webster KE, Kvist J. The impact of psychological readiness to return to sport and recreational activities after anterior cruciate ligament reconstruction. Br J Sports Med. 2014;48(22):1613-9.
80. Renstrom P, Ljungqvist A, Arendt E, et al. Non-contact ACL injuries in female athletes: an International Olympic Committee current concepts statement. Br J Sports Med. 2008;42(6):394-412.
81. Myklebust G, Bahr R. Return to play guidelines after anterior cruciate ligament surgery. Br J Sports Med. 2005;39(3):127-31.
82. Paterno MV, Thomas S, VanEtten KT, Schmitt LC. Confidence, ability to meet return to sport criteria, and second ACL injury risk associations after ACL-reconstruction. J Orthop Res. 2022;40(1):182-90.
83. Ihalainen JK, Mikkonen RS, Ackerman KE, et al. Beyond menstrual dysfunction: does altered endocrine function caused by problematic low energy availability impair health and sports performance in female athletes? Sports Med. 2024;54(9):2267-89.
84. Henry JC, Kaeding C. Neuromuscular differences between male and female athletes. Curr Womens Health Rep. 2001;1(3):241-4.
85. Sutton KM, Bullock JM. Anterior cruciate ligament rupture: differences between males and females. J Am Acad Orthop Surg. 2013;21(1):41-50.
86. Cheung EC, Boguszewski DV, Joshi NB, Wang D, McAllister DR. Anatomic factors that may predispose female athletes to anterior cruciate ligament injury. Curr Sports Med Rep. 2015;14(5):368-72.
87. Herzberg SD, Motu'apuaka ML, Lambert W, Fu R, Brady J, Guise JM. The effect of menstrual cycle and contraceptives on ACL injuries and laxity: a systematic review and meta-analysis. Orthop J Sports Med. 2017;5(7):2325967117718781.
88. Dragoo JL, Castillo TN, Braun HJ, Ridley BA, Kennedy AC, Golish SR. Prospective correlation between serum relaxin concentration and anterior cruciate ligament tears among elite collegiate female athletes. Am J Sports Med. 2011;39(10):2175-80.
89. Mountjoy M, Sundgot-Borgen J, Burke L, et al. The IOC consensus statement: beyond the Female Athlete Triad—Relative Energy Deficiency in Sport (RED-S). Br J Sports Med. 2014;48(7):491-7.
90. Crossley KM, Patterson BE, Culvenor AG, Bruder AM, Mosler AB, Mentiplay BF. Making football safer for women: a systematic review and meta-analysis of injury prevention programmes in 11 773 female football (soccer) players. Br J Sports Med. 2020;54(18):1089-98.
91. John G, AlNadwi A, Georges Abi Antoun T, Ahmetov II. Injury prevention strategies in female football players: addressing sex-specific risks. Sports (Basel). 2025;13(2):39.
92. Geertsema C, Geertsema L, Farooq A, et al. Injury prevention knowledge, beliefs and strategies in elite female footballers at the FIFA Women's World Cup France 2019. Br J Sports Med. 2021;55(14):801-6.
93. Seidman L, Seidman DS, Constantini NW. Hormonal contraception for female athletes presents special needs and concerns. Eur J Contracept Reprod Health Care. 2024;29(1):8-14.
94. Gray AM, Gugala Z, Baillargeon JG. Effects of oral contraceptive use on anterior cruciate ligament injury epidemiology. Med Sci Sports Exerc. 2016;48(4):648-54.
95. Barlow A, Blodgett JM, Williams S, Pedlar CR, Bruinvels G. Injury incidence, severity, and type across the menstrual cycle in female footballers: a prospective three season cohort study. Med Sci Sports Exerc. 2024;56(6):1151-8.